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Weight-centric prevention of cancer

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ABSTRACT

Background: The link between excess adiposity and carcinogenesis has been well established for multiple malignancies, and cancer is one of the main contributors to obesity-related mortality. The potential role of different weight-loss interventions on cancer risk modification has been assessed, however, its clinical implications remain to be determined. In this clinical review, we present the data assessing the effect of weight loss interventions on cancer risk.

Methods: In this clinical review, we conducted a comprehensive search of relevant literature using MEDLINE, Embase, Web of Science, and Google Scholar databases for relevant studies from inception to January 20, 2024. In this clinical review, we present systematic reviews and meta-analysis, randomized clinical trials, and prospective and retrospective observational studies that address the effect of different treatment modalities for obesity in cancer risk. In addition, we incorporate the opinions from experts in the field of obesity medicine and oncology regarding the potential of weight loss as a preventative intervention for cancer.

Results: Intentional weight loss achieved through different modalities has been associated with a reduced cancer incidence. To date, the effect of weight loss on the postmenopausal women population has been more widely studied, with multiple reports indicating a protective effect of weight loss on hormone-dependent malignancies. The effect of bariatric interventions as a protective intervention for cancer has been studied extensively, showing a significant reduction in cancer incidence and mortality, however, data for the effect of bariatric surgery on certain specific types of cancer is conflicting or limited.

Conclusion: Medical nutrition therapy, exercise, antiobesity medication, and bariatric interventions, might lead to a reduction in cancer risk through weight loss-dependent and independent factors. Further evidence is needed to better determine which population might benefit the most, and the amount of weight loss required to provide a clinically significant preventative effect.

1. Introduction

The burden of obesity and its associated comorbidities has been steadily increasing to reach epidemic proportions. It has been estimated that by 2030, around 20% of the world's adult population will have obesity, with a more rapid and steep increase in prevalence in developing regions [1]. Remarkably, in the United States, the prevalence of obesity is expected to increase from 42% (2017 prevalence) to 50% by 2030 [2]. A study reported that the global disability-adjusted life years attributable to high body mass index (BMI) have nearly doubled from 1990 to 2017 in women (33.1 million to 70.7 million) and men (31.9 million to 77.0 million), mostly related to an increase in cardiovascular disease, diabetes, kidney disease, and cancer [3].

Notably, a substantial proportion of malignancies can be attributed to a high BMI [4]. For instance, in 2014, out of all new cancer diagnoses in the United States, about 40% were obesity-associated malignancies, disproportionately affecting women and people aged >50 years [5]. According to the International Agency for Research on Cancer (IARC), there is sufficient evidence to indicate a relation between excess adiposity and cancer in the following anatomical sites: esophageal, gastric cardia, colorectal, liver, gallbladder, pancreas, breast (in post-menopausal patients), endometrium, ovary, kidney, meningioma, thyroid, and the bone marrow (multiple myeloma) (Fig. 1) [6]. Additionally, there is data indicating a probable relationship for advanced prostate cancer [7], and limited evidence for male breast cancer [8] and

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Abbreviations

BMI	Body Mass Index
IARC	International Agency for Research on Cancer
WHI	Women's Health Initiative
HR	Hazard Ratio
95% CI	95% Confidence Interval
ILI	Intensive Lifestyle Intervention
AOM	Antiobesity Medication
RR	Risk Ratio
IL	Interleukin
hsCRP	High-sensitivity C-reactive protein
FDA	U.S. Food and Drug Administration
MTC	Medullary Thyroid Cancer
GIP	Glucose-dependent insulinotropic polypeptide
GLP-1	Glucagon-like Peptide-1
SOS	Swedish Obese Subject (SOS) study
RYGB	Roux-en-Y Gastric Bypass
SG	Sleeve Gastrectomy
ccRCC	Clear Cell Renal Cell Carcinoma
MC4R	Melanocortin-4 Receptor
MEN-2	Multiple Endocrine Neoplasia Type 2 Syndrome

diffuse large B-cell lymphoma [9].

With the rate of obesity increasing at an alarming pace [10], multiple treatment modalities have been developed, including lifestyle interventions, antiobesity medications, and bariatric procedures, with the ultimate goal of achieving sufficient weight loss to decrease the risk of developing adiposity-associated diseases, or improve their outcomes if present [11]. As some cancers have a strong association with excess adiposity, promoting evidence-based and individualized treatments for overweight and obesity could therefore contribute to their prevention. In this review, we present data on the protective effect of treatment modalities for overweight and obesity on the risk of developing cancer.

2. Methods

In this clinical review, we explore the role of treatment modalities for overweight and obesity as a potential preventative intervention for certain types of cancer. We searched the MEDLINE, Embase, Web of Science, and Google Scholar databases for relevant studies from inception to January 20, 2024, in English language. We present publications (e.g., systematic reviews and meta-analysis, randomized clinical trials, and prospective and retrospective observational studies) that focus on the effect of treatment modalities for overweight and obesity in cancer prevention. We included the following treatment modalities: lifestyle interventions (medical nutrition therapy and exercise), antiobesity medications, and bariatric procedures. We also present an expert opinion regarding weight-centric prevention of cancer.

3. Results

3.1. Effects of excess adiposity in carcinogenesis

Multiple mechanisms have been proposed to explain the relationship between excess adiposity and cancer. The contribution of each mechanism to carcinogenesis varies by the anatomic site involved and by the presence of specific defining characteristics in a population [12]. The interplay of different mechanisms leading to malignancy in patients with excess adiposity is being actively studied. In Table 1, we summarize the currently proposed pathogenic and molecular mechanisms underlying

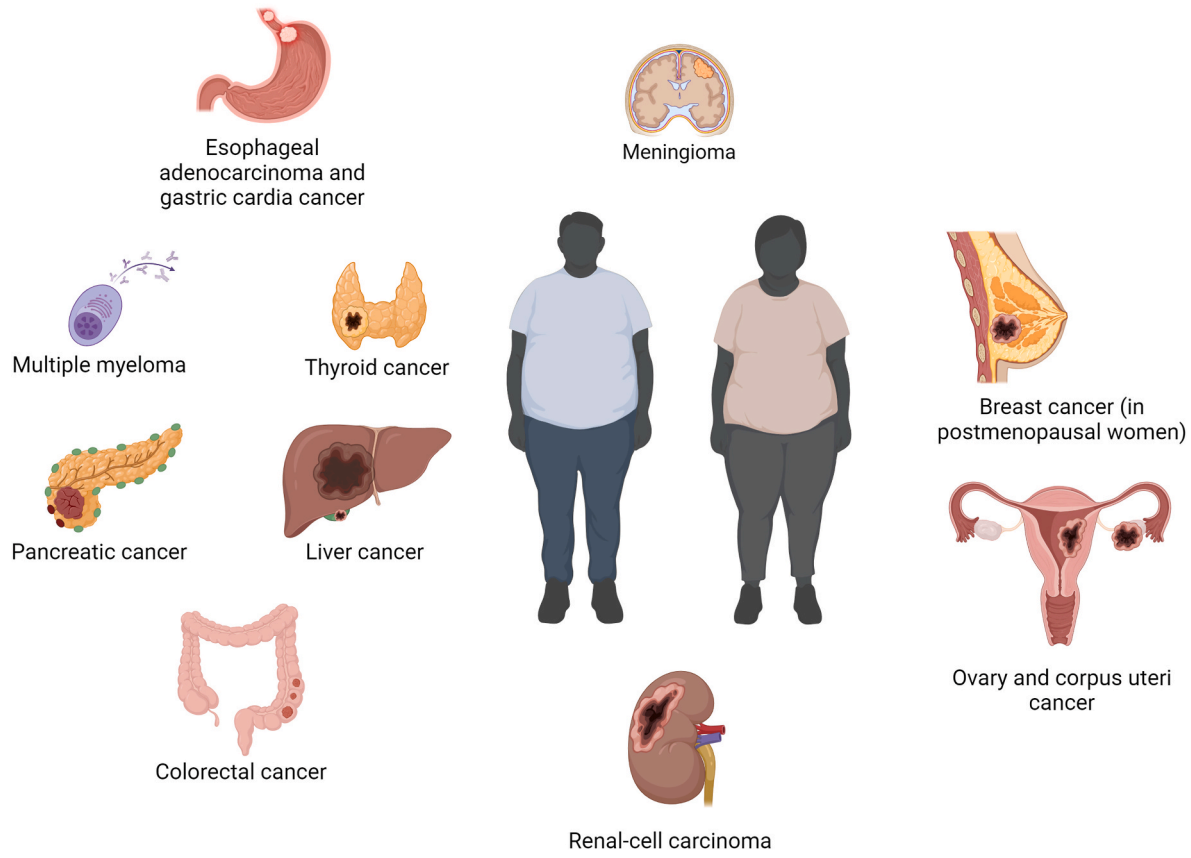

Fig. 1. Anatomical sites with strong evidence for association with excess adiposity as established by the International Agency for Research on Cancer.

Table 1
Mechanisms of carcinogenesis for obesity-associated cancers.

Cancer site	Adiposity-associated pathogenic mechanisms	Proposed adiposity-associated molecular mechanisms for carcinogenesis
Esophageal adenocarcinoma [124–127]	Abdominal adiposity predisposes to gastroesophageal reflux disease, increasing the risk of Barrett's esophagus and esophageal adenocarcinoma. Additional contributors: chronic inflammation and hyperinsulinemia.	Increased expression of leptin receptors in patients with obesity and esophageal adenocarcinoma could stimulate proliferation and inhibit apoptosis in esophageal adenocarcinoma cells, promoting progression of the disease. Hyperinsulinemia in vivo leads to IGF-1 receptor upregulation and promotion of esophageal carcinogenesis through cell growth and proliferation.
Gastric cardia [128–132]	Chronic inflammation and hyperinsulinemia.	Malignant gastric cells have higher expression of IGF-1, which could promote cell proliferation. There is correlation between leptin levels and leptin tissue expression and clinicopathological variables in gastric cancer, suggesting its carcinogenic role. IL-mediated chronic inflammation could contribute to cell proliferation and invasion.
Colorectal [133–137]	Chronic inflammation and hyperinsulinemia.	Chronic inflammation related to visceral adiposity may participate tumorigenesis and immune escape, leading to cancer development and progression. Leptin and other adipokines potentially induce growth of neoplastic colorectal cells. Insulin and IGF-1 signaling favors mitogenic and proangiogenic signals in colorectal.
Liver [138–141]	Chronic inflammation, hyperinsulinemia, and alterations in the gut microbiome.	Adiposity induced proinflammatory cytokines, such as TNFα and IL-6 might contribute to liver tumorigenesis. Obesity-associated alterations in gut microbiome metabolites might contribute to DNA damage and activation of a senescence-associated secretory phenotype in hepatic stellate cells, essential for liver tumorigenesis. Insulin and IGF-1 signaling in the liver might contribute to liver tumorigenesis.
Gallbladder [142,143]	Chronic inflammation from gallstones, which patients with obesity are at risk of.	Not widely studied.
Pancreas [144–149]	Chronic inflammation and hyperinsulinemia.	Adipokines and other adiposity-associated inflammatory mediators activate oncogenic downstream pathways. Insulin and IGF-1 stimulate pancreatic duct acinar cell proliferation through mTOR signaling.
Breast (post-menopausal), Endometrium and Ovary [16,150–160]	Hyperestrogenism, chronic inflammation, oxidative stress, and hyperinsulinemia.	Excess adiposity and its associated inflammatory environment increase adipose-tissue aromatase expression and activity, leading to androgen conversion to estrogen. Estrogen and insulin/IGF-1 are major synergistic mitogens for epithelial cells, inducing cell cycle progression. Excess adiposity promotes oxidative stress, which denatures cell structures leading to genetic instability and tumorigenesis. Leptin stimulates breast, endometrial, and ovarian cancer cell growth and impairs apoptosis through activation of multiple signaling pathways. In addition, leptin increases the expression of aromatase, further contributing to hyperestrogenism.
Clear Cell Renal cell carcinoma (ccRCC) [161–164]	Microenvironment alterations, metabolic reprogramming, and chronic inflammation.	Genes associated with an increased risk of ccRCC are associated with metabolic stress pathways. Lipidomic signatures of ccRCC contributes to cell proliferation. Expression of different adipokines has been suggested to modify the risk for ccRCC.
Meningioma [165–169]	Hyperestrogenism.	Excess adiposity and its associated inflammatory environment increase adipose-tissue aromatase expression and activity, leading to androgen conversion to estrogen. Most meningiomas express progesterone, estrogen, or androgen receptors, and estrogen is a potent enhancer of meningioma cell proliferation in vitro.
Thyroid [170–177]	Chronic inflammation. Possibly hyperinsulinemia and hyperestrogenism, although their roles are less well defined.	Increased adipokines and oxidative stress promote malignancy. In vitro, insulin promotes thyroid cell proliferation and migration, and insulin resistance correlates with thyroid nodule vascularity. There is increased estrogen α-receptor expression in thyroid cancer cells, especially in post-menopausal women. Its role is unclear.
Multiple myeloma [178–182]	Chronic inflammation. Possibly hyperinsulinemia although its role is less well defined.	Increase in bone marrow adipose tissue leads to increased circulating adipokines.

(*continued on next page*)

Table 1 (*continued*)

Cancer site	Adiposity-associated pathogenic mechanisms	Proposed adiposity-associated molecular mechanisms for carcinogenesis
		In vivo and in vitro studies show increased adipocyte-secreted cytokine angiotensin II promotes tumorigenesis. Insulin is a potent growth factor for multiple myeloma cells in vitro.

an increased malignancy risk by anatomic site for obesity-associated cancers, as established by the IARC [6].

The adipose tissue is a highly active endocrine organ responsible for secreting multiple adipokines that regulate essential processes such as energy homeostasis and inflammation [13]. For instance, adiponectin is an insulin-sensitizing and anti-inflammatory adipokine [14]. Hypoadiponectinemia is present among patients with obesity and has been associated with an increased risk of malignancy, due to alterations in receptor-mediated signaling pathways, insulin sensitivity, inflammatory response, and angiogenesis [15]. In contrast, high leptin and visfatin levels, two other adipokines, have also been implicated in tumorigenesis [16]. Similarly, alterations in adipose tissue maturation might contribute to low-grade chronic inflammation, resulting in the release of multiple proinflammatory cytokines and angiogenic factors, that could contribute to carcinogenesis in multiple anatomic sites [17]. Although data is inconclusive, alterations in gut microbiota in patients with obesity might further promote chronic inflammation and the risk for developing cancer [18,19]. Moreover, adipose tissue within the tumor microenvironment might contribute to carcinogenesis by secretion of signaling molecules and by providing an energy reservoir for proliferating cells [20,21].

Notably, adiposity associated diseases can also increase the risk of malignancy. For instance, abdominal obesity predisposes to gastroesophageal reflux disorder and Barrett's esophagus due to increased intra-abdominal pressure [22]. However, in the case of gastroesophageal reflux, as it does not fully explain the increased risk of esophageal adenocarcinoma in patients with obesity, it has been hypothesized that adipose tissue-mediated inflammation might contribute to dysplastic and neoplastic progression [23,24].

To conclude this section, while we present data on the risk of cancer in patients with increased adiposity, it is important to note that some observational studies have reported that patients with higher BMI might have a decreased risk for certain types of cancer, including breast cancer in premenopausal patients [25,26]. This controversial epidemiological phenomenon has been named the 'obesity paradox' [27]. The mechanism underlying this protective effect has not been completely elucidated. Finally, the effect of intentional weight loss on certain biomarkers associated to cancer have shown to be small or inconsistent, and as a result, merit further investigation [28].

3.2. Role of intentional weight loss in cancer prevention

Considering the strong association between excess adiposity and certain types of cancer, multiple studies have assesed the effect of intentional weight loss in cancer risk. One of the most studied populations is postmenopausal women [29–32]. For instance, the observational study branch of the Women's Health Initiative (WHI), which included 93,676 postmenopausal women across the US, has provided valuable information [33,34]. In this study, postmenopausal women who intentionally achieved at least a 5% reduction in total body weight over a 3-year follow-up had a significantly lower risk of obesity-associated cancers as compared to women with stable weight (HR: 0.88, 95%CI: 0.80–0.96, P < 0.05) [35]. A stratified analysis by BMI showed that this effect was only present among women with obesity [35]. This protective effect was exemplified with endometrial cancer. Postmenopausal women that achieved a weight loss of at least 5% had a significantly lower risk of endometrial cancer, with a stronger association among women that had obesity at baseline [36]. In addition, women that gained at least 10 pounds of total body weight over a 3-year period had a significantly higher risk of endometrial cancer [36]. In accordance with the WHI data, results from the Iowa Women's Health Study showed that postmenopausal women that intentionally lost at least 20 pounds during adulthood had a 18% reduced incidence of obesity-associated cancers [37]. Moreover, a pooled analysis including ten prospective cohorts from multiple countries showed that sustained weight loss led to a decreased risk of breast cancer in women aged over 50 years not taking menopausal hormonal therapy [38]. These findings suggest that weight loss could be a preventative intervention for obesity-associated cancer in postmenopausal women, yet, the effects of intentional weight loss in other populations have not been completely elucidated.

Outside of studies in postmenopausal women, the Look AHEAD trial gave some insight in the effect of weight loss in patients with type 2 diabetes. In this trial, individuals with overweight or obesity and type 2 diabetes mellitus were randomized to either conventional diabetes education or an intensive lifestyle intervention (ILI) to promote weight loss [39]. Even though this trial was initially conceived to assess for improvement in cardiovascular outcomes, a subsequent analysis was done to evaluate the effect of the ILI in the risk of cancer. Compared to patients receiving conventional diabetes education, patients that were randomized to the ILI had a greater weight loss at 1 year (8.6% vs. 0.7%), and had a lower incidence of obesity-associated cancers (6.1 vs. 7.3 cases per 1000 person-years; HR: 0.84, 95% CI: 0.58–1.04) [40]. It is important to note that the difference in cancer risk was not statistically significant for the duration of the follow-up (median: 11 years), likely due to inadequate statistical power or misclassification of cancer location. Notably, sex did not affect the effect of the ILI on cancer risk ($p = 0.68$) [40].

Weight cycling (i.e., repeated cycles of intentional weight loss followed by weight regain) is common among people with overweight or obesity, with a study reporting that 42% of men and 57% of women had experienced at least one episode of weight cycling throughout their adult lives [41]. Contrary to weight loss maintenance, some studies have suggested that weight cycling could contribute to an increased risk of cancer by promoting an inflammatory state and altering immune surveillance [42–44]. However, results from a large prospective cohort study showed that after adjusting for BMI and other covariates, weight cycling was not associated with an increased risk of cancer in men (HR:0.96, 95% CI: 0.83–1.11) or women (HR:0.96, 95% CI: 0.86–1.08), regardless of a history of obesity [45]. Importantly, this study reported that weight cycling was not protective against cancer [45]. Prevention of weight regain is essential after the implementation of any weight loss intervention, and long-term management might be needed to prevent further episodes of weight cycling in some patients.

3.3. Effect of weight loss interventions on cancer risk

Given the effect of intentional weight loss in relation to cancer risk reduction, we will now summarize the evidence of different weight loss interventions on cancer risk, including lifestyle interventions (i.e., medical nutrition therapy and exercise), antiobesity medications (AOMs), and bariatric surgery.

3.3.1. Lifestyle interventions

3.3.1.1. Medical nutrition therapy. A meta-analysis including 8 randomized clinical trials suggests that diet-induced weight loss leads to a

modest, but non statistically significant decreased risk of cancer mortality (pooled RR: 0.58, 95% CI: 0.30–1.11) [46]. In the same study, nineteen trials had very low quality evidence for patients developing new cancer, with only 103 events reported among 6330 participants, highlighting the low number of events in these trials. Besides this, due the limited follow-up duration for these trials and the significant heterogeneity in weight loss outcomes, further large-scale studies with a longer follow-up duration are required to better elucidate the effects of diet-induced weight loss in the reduction of cancer risk.

Although the data assessing the effect of weight loss from dietary interventions in cancer risk is not conclusive, previous interventional studies have demonstrated that weight loss achieved through diet leads to a decrease in multiple biomarkers associated with cancer [47]. For instance, diet-induced weight loss in a cohort of 10 premenopausal women with obesity led to significant reduction in serum tumor necrosis factor-α and interleukin (IL)-8 concentrations, while also down-regulating the expression of pro-inflammatory cytokines and gene pathways associated with colorectal cancer in rectosigmoid biopsies [48]. Similarly, in a trial including 20 participants with obesity, an 8-week calory-restricted liquid diet leading to substantial weight loss (13.6%) was associated with a significant decrease in colonic tissue expression of Ki-67, an important cell proliferation marker [49]. In accordance with these data, a trial in postmenopausal women showed that a dietary intervention led to a reduction in body weight and favorable hormonal changes that could reduce the risk of breast cancer, including a decrease in total and free serum testosterone levels, and an increase in sex hormone binding globulin and IGF binding protein 1 and 2 [50].

There is data suggesting that dietary macronutrient composition could affect cancer risk [51]. For instance, previous studies have reported that increased consumption of red meat and processed meat have a strong association with colorectal cancer [52,53]. The Mediterranean diet, a dietary pattern consisting of high amounts of fruits, vegetables, whole grains, cereals, nuts, legumes, fish, and extra virgin olive oil, and reduced consumption of red meats, has been associated with a decreased risk of cancer in some observational and prospective studies [54,55]. A meta-analysis including 56 observational studies showed that high-adherence to a Mediterranean diet led to a reduction in overall cancer mortality and a decrease in the incidence of colorectal, breast, gastric, prostate, liver and head and neck cancer [56]. The effect of other dietary patterns has not been as widely studied.

The clinical implications of these findings remain to be determined. Currently, a caloric deficit of 500–750 kcal/d, usually achieved with a daily calory intake of 1200–1500 kcal for women and 1500–1800 kcal for men, is recommended to promote weight loss in patients with overweight or obesity [57,58]. With this information in mind, a comprehensive dietary approach incorporating caloric restriction to promote weight loss while preserving a healthy diet composition pattern can become a valuable cancer preventative strategy for people with overweight or obesity.

3.3.1.2. Physical activity. Previous reports have suggested that the addition of exercise training to hypocaloric diet leads to a more significant reduction in inflammatory biomarkers associated to malignancy in postmenopausal women, including C-reactive protein and IL-6 [59]. A clinical trial randomized 439 postmenopausal women with overweight or obesity to different lifestyle interventions: a) caloric restriction diet, b) aerobic exercise, c) combined diet + exercise or d) control [60]. After 1 year, the diet + exercise, diet, and exercise group lost 10.8%, 8.5% and 2.4% of their body weight, respectively. When compared to controls, the diet, and the diet + exercise group, had a significant decrease in most studied inflammatory biomarkers, however, this effect was not present for the exercise group [60]. In addition, only patients that lost ≥5% of their weight in the diet and diet + exercise group had a significant reduction in high-sensitivity C reactive protein (hs-CRP) [60]. In a similar study, 243 postmenopausal women with overweight or obesity were randomized to either a 16-week intervention consisting of either diet only (caloric restriction of 3500 kcal/week with habitual physical activity level), diet + exercise (caloric deficit of 1750 kcal/week with an intensive physical activity regimen consisting of a 4 h/week combined endurance and strenght exercise program), or no intervention (i.e., habitual diet and physical activity level) [61]. The diet and the diet + exercise groups lost 6.1% and 6.9% of their body weight, respectively. When compared to controls, leptin levels significantly decreased for both groups. In contrast, the hsCRP levels decreased for both groups, but results were only significant for the diet + exercise group [61]. Moreover, data from prospective and interventional studies suggest that increased physical activity levels are associated with decreased serum estrogen and testosterone levels in postmenopausal women which can consequnetly decrease estrogen-associated cancers in this population [62–66].

Currently, comprehensive lifestyle intervention programs usually recommend increasing aerobic physical activity for ≥150 min/wk, however, levels closer to 225–420 min/wk might be needed to lose 5–7.5 kg, and 200–300 min/wk might be needed to avoid weight regain in the long-term [67]. Although there is no conclusive evidence showing the direct effect of exercise in cancer risk reduction, these data suggest that the addition of exercise to medical nutrition therapy as part of a comprehensive weight loss intervention, can result in a more favorable reduction in inflammatory and hormonal biomarkers associated with the development of obesity-associated cancers.

Medical nutrition therapy and exercise continue to be the backbone of comprehensive weight management programs, however, substantial and durable weight loss might be difficult to achieve in a significant proportion of patients with this methods alone. For instance, about 60% of patients do not achieve a total body weight loss percentage of at least 10% with currently recommended caloric deficits [68]. Hence, multiple patients with obesity require pharmacological and/or surgical interventions to achieve clinically significant weight loss.

3.3.2. Antiobesity medications

AOM are an effective treatment for overweight and obesity. AOMs not only induce weight loss, but if used correctly, i.e., long-term, can also promote weight loss maintenance. The use of AOMs has increased in the US over the past few years, however, access to these medications remains limited, mostly due to inadequate insurance coverage and high costs for patients [69–73]. At the time of this review, the Food and Drug Administration (FDA) has approved the use of seven different agents for chronic overweight and obesity treatment. Even though the effect of AOMs in the risk of developing cancer has not been directly examined, the efficacy of AOMs to promote weight loss as part of a comprehensive weight loss intervention has been well established [74,75]. As with other weight loss interventions, there is significant heterogeneity in weight loss outcomes among different AOMs and even within the same AOM [76]. Newer glucagon-like peptide-1 (GLP-1) receptor agonists (i.e., semaglutide) and glucose-dependent insulinotropic polypeptide (GIP) co-agonists (i.e., tirzepatide) have showed significantly superior weight loss outcomes in comparison to other antiobesity medications [77,78]. In Table 2, we show the reported weight loss outcomes and evidence on potential interactions with cancer risk of FDA-approved AOMs for chronic weight management.

AOMs are a safe intervention, with most reported adverse events being mild or moderate, usually self-resolving, and generally not leading to medication discontinuation [76]. Out of the currently FDA-approved AOMs, concerns have been raised about the risk of medullary thyroid cancer (MTC) with GLP-1 receptor agonists, liraglutide, semaglutide and tirzepatide. Reports from studies with rodents suggested that GLP-1 receptor agonists led to thyroid C-cell proliferation, with an increased risk of malignancy [79]. This resulted in the FDA issuing a boxed warning for all GLP-1 receptor agonist, and a contraindication for patients with a personal or family history of MTC or Multiple Endocrine

Table 2
Antiobesity medications approved by the Food and Drug Administration for chronic weight management.

Antiobesity medication	Mechanism of action	Reported total body weight loss percentage	Potential interactions with cancer risk
Orlistat [183–190]	Lipase inhibitor.	10.2%	In vitro study suggested that orlistat induced caspase-dependent apoptosis and protective autophagy in ovarian cancer cells. In vitro and in vivo studies suggest that orlistat led to decreased colonic inflammation and cancer cell proliferation. Orlistat is a fatty acid synthase inhibitor, potentially having antiproliferative effects.
Phentermine –Topiramate [191,192]	Appetite suppressant.	6.7%–14.4%	An in vitro study suggested that topiramate inhibited proliferation and promoted apoptosis in ovarian cancer cells.
Naltrexone – bupropion [193–196]	Appetite suppressant.	6.7%–11.5%	In vitro and in vivo studies have suggested that low-dose naltrexone might promote apoptosis and inhibit proliferation of colorectal cancer cells and cervical cancer cells.
Setmelanotide[a] [197]	Melanocortin 4 receptor (MC4R) agonist.	12.5%–25.6%	Half of patients treated with setmelanotide develop skin hyperpigmentation disorders. Melanoma has been proposed as a potential risk and is actively being monitored. Subjects with a history or close family history of melanoma were excluded from clinical trials. To date, no evidence exists of an increased risk of melanoma in patients treated with setmelanotide.
Liraglutide [79,198,199]	Glucagon-like peptide 1 (GLP-1) receptor agonist.	6.2%–8.0%	Concerns have been raised about the possibility of increased risk of medullary thyroid cancer (MTC) and pancreatic cancer with the use of GLP-1 receptor agonists.
Semaglutide [77,88,89,200]		9.6%–14.9%	While data from animal models have suggested a possible connection between the use of GLP-1 receptor agonists and MTC, the risk of MTC in humans with the use of these medications has not been established clinically. Currently, GLP-1 receptor agonists are contraindicated in patients with a personal or family history of MTC or multiple endocrine neoplasia type 2 syndrome (MEN2).
Tirzepatide [78,201]	GLP-1 and Glucose-dependent insulinotropic polypeptide (GIP) dual agonist.	14.7%–20.9%	Evidence suggests that the risk of pancreatic and thyroid cancer, and overall neoplasias are not increased in patients using GLP-1 receptor agonists.

[a] Setmelanotide has been approved for chronic weight loss management in patients with select genetic variants in the leptin-melanocortin pathway.

Neoplasia syndrome type 2, a known genetic syndrome associated with MTC. Some reports have suggested a disproportionately higher proportion of thyroid malignancies in patients receiving GLP-1 receptor agonists [80–82], however, a meta-analysis including data from 45 trials of different GLP-1 receptor agonists concluded that there was no significant effect on thyroid cancer risk (RR: 1.30, 95% CI: 0.86–1.97) [83]. In addition, a study that randomized 9340 patients with type 2 diabetes to either liraglutide or placebo reported that liraglutide did not significantly increase calcitonin levels at 36 months, with no episodes of C-cell hyperplasia or MTC in patients treated with liraglutide [84]. Similarly, a concern for an increased risk of pancreatic cancer with the use of GLP-1 receptor agonists has been raised, as some studies in animal models showed that incretin-based therapies led to pancreatic acinar and duct cell proliferation [85,86]. Previous meta-analyses found that there is no increased risk of pancreatic cancer in patients taking GLP-1 receptor agonists [87,88]. Moreover, a recent meta-analysis including data from 37 randomized clinical trials and 19 real world-studies with 46,719 patients showed that compared to placebo, semaglutide was not associated with an increased risk of pancreatic cancer (OR: 0.25, 95% CI: 0.03–2.24, $p = 0.21$), thyroid cancer (OR: 2.04, 95% CI: 0.33–12.61, $p = 0.82$) or all neoplasias (OR: 0.95, 95% CI: 0.44–1.89) [89].

The selection of an antiobesity medication as an added tool for obesity treatment remains a clinical challenge. A recent report by the Institute for Clinical and Economic Review suggested that semaglutide was the most effective AOM, however, in terms of cost-effectiveness phentermine-topiramate was a superior alternative [90]. In this context, an individualized shared-decision making approach taking into consideration comorbidities, safety profile, insurance coverage and patient preferences might be required to optimize weight loss response [91].

3.3.3. *Bariatric surgery*

3.3.3.1. Overall effect of bariatric surgery in cancer risk. Bariatric surgery remains the most effective intervention for obesity, often leading to substantial and durable weight loss and comorbidity resolution [92]. Previous studies have shown a decreased incidence and mortality rate associated with cancer in people with obesity undergoing bariatric surgery [93–96]. A meta-analysis including 32 studies showed that bariatric surgery was associated with a significant reduction in the overall incidence of cancer (RR: 0.62, 95% CI: 0.46–0.84, $P = 0.002$) and cancer-related mortality (RR: 0.51, 95% CI: 0.42–0.62, $p < 0.001$), however it should be noted that almost two-thirds of the studies included for this review had a serious or critical risk of bias, and there was significant heterogeneity among included studies [97]. A prospective intervention trial in Sweden, the Swedish Obese Subject (SOS) study, followed 4047 participants with obesity, out of which 2010 underwent bariatric surgery, and 2037 served as matched controls [98]. During the follow-up period, 286 new cases of cancer occurred, 117 and

169 in the surgery and the control group, respectively. Patients that underwent bariatric surgery had a lower risk of incident cancer when compared to the control group (HR: 0.67, 95% CI: 0.53–0.85, p = 0.0009). A differential effect was observed depending on sex. While authors reported a significant decrease in risk of incident cancer in women (HR: 0.58, 95% CI: 0.44–0.77, p = 0.0001), this was not the case for men (HR: 0.97, 95% CI: 0.61–1.52, p = 0.90) [98]. Similarly, a meta-analysis including eight population-based studies reported that bariatric surgery led to a lower risk of developing obesity-associated and overall cancer incidence, however, after stratifying by sex, the effect of bariatric surgery was less prominent in men [99]. This diverging effects according to sex could be the result of the strong protective effect of weight loss on hormone-dependent breast and endometrial cancer, which represent a significant proportion of cancers in postmenopausal women [95]. It is important to note that, Schauer et al. demonstrated that weight loss at one year was an independent predictor of cancer risk reduction, while bariatric surgery by itself was not; with an estimated 14% decrease in cancer risk for every 10% of body weight loss [100]. These results suggest that the reduction of cancer risk in patients undergoing bariatric surgery is mostly weight-dependent, but potential weight-independent metabolic benefits of bariatric surgery in cancer risk remain unclear [101].

3.3.3.2. Effect of bariatric surgery on cancer by anatomic site. The protective effect of bariatric surgery for hormone-related malignancies has been more widely studied [102–105]. A meta-analysis including seven prospective and retrospective cohort studies showed that bariatric surgery led to a 59% reduction in the aggregate risk of breast, ovarian, and endometrial cancer (RR: 0.41, 95% CI: 0.31,0.56, p < 0.05) [102]. Moreover, Feigelson et al. showed that bariatric surgery led to a reduction in premenopausal and postmenopausal breast cancer cases, with a more prominent effect for estrogen-receptor negative breast cancer in premenopausal women, and estrogen-receptor positive breast cancer for postmenopausal women [106]. These protective effects could be attributed to weight-loss induced favorable alterations in sex hormone parameters [50,107].

Similarly, in a recent study, Clapp et al. assessed the effect of bariatric surgery on non-hormone related cancer (i.e., excluding breast, endometrium, ovary, prostate, testis, thyroid, and osteosarcoma) [94]. This meta-analysis included 15 retrospective studies, and showed that bariatric surgery led to a decrease incidence of non-hormone related cancer when compared to the non-surgical group (OR: 0.65, 95% CI: 0.53,0.80, p < 0.002) [94]. Wilson et al. reported that bariatric surgery led to a reduction in the incidence of hepatocellular, colorectal, pancreatic and gallbladder cancer, and female-specific hormone dependent cancers (i.e., breast, endometrial and ovarian cancer), without evidence for a protective effect on the incidence of esophageal, gastric, thyroid, kidney and prostate cancer or multiple myeloma [97].

The effect of bariatric surgery in the risk of developing colorectal cancer has been a subject of controversy, as data from observational studies has shown discordant results [108–116]. A population-based cohort study indicated that Roux-en-Y gastric bypass (RYGB), but not banding or sleeve gastrectomy, led to an increased risk of colorectal cancer (OR: 2.63, 95% CI: 1.17–5.95, P < 0.05) [111]. It has been hypothesized that bariatric surgery-induced alterations in microbiome and increased bile salt exposure might lead to local mucosal changes that favor carcinogenesis in the colon [117–119]. However, a recent meta-analysis including 13 retrospective studies, and a population of over 3 million, indicated a decreased risk of developing colorectal cancer in patients undergoing bariatric surgery, with a pooled RR of 0.63 (95% CI: 0.50–0.79, P < 0.05) [120]. The effect of bariatric surgery on colorectal cancer remains unclear, and additional studies with longer follow-up periods are required to assess this. Overall, there is evidence favoring the protective effect of bariatric surgery in the risk of liver, breast, endometrium, ovary, and pancreas cancer, however, it is worth mentioning that most of the studies assessing the risk for future cancer after bariatric surgery have been retrospective in nature, with follow-up time often being insufficient. The significant heterogeneity and high risk of bias for most of these studies limit the conclusions that can be drawn, and further studies are needed to better assess the potential protective effect of bariatric surgery in other types of cancer [97].

3.3.3.3. Differential effect among bariatric interventions. Currently, the most frequently performed bariatric surgeries in the United States are the sleeve gastrectomy (SG) and the RYGB [121]. Significant heterogeneity has been reported in weight loss outcomes of these two interventions. The RYGB results in greater weight loss compared to the SG, but carries a higher burden of complications [122]. The differential effect of different types of bariatric surgeries on cancer risk has been previously examined.

Within the SOS study cohort, a significantly lower risk of incident cancer was present in women undergoing gastric banding (HR: 0.54, 95% CI: 0.31–0.93, p = 0.026) and vertical banded gastroplasty (HR: 0.60, 95% CI: 0.44–0.82, p = 0.0012), but not in women undergoing RYGB or men undergoing any of these surgical interventions [98]. In contrast, other studies have reported that within bariatric surgeries, RYGB led to a greater reduction in obesity-related cancers than the sleeve gastrectomy and gastric banding [94,111].

More recently, multiple endoscopic bariatric and metabolic therapies have been proposed as non-invasive and efficacious interventions for weight management, with options including the intragastric balloon and the endoscopic sleeve gastroplasty [123]. The effect of these endoscopic interventions on cancer risk has not been assessed directly.

4. Expert opinion: weight-centric approach to cancer prevention

It is now well established that overweight and obesity in adulthood is a risk factor for many cancers [6]. This likely involves increased inflammation from visceral fat, increased insulin levels, insulin-like growth factors, and increased sex hormones. It is astounding that more than 40% of women and 35% of men in the United States live with obesity, with projections of its prevalence continuing to rise. The rates vary among different racial and ethnic groups, with a higher incidence of obesity seen in Non-Hispanic Blacks, American Indian/Pacific Islanders, and Hispanics. Concerningly, rates of obesity in children are also increasing across the world. Despite the knowledge that obesity increases the risk of cancer, cardiovascular disease, and diabetes/metabolic disorders, rates continue to rise. This is likely due to the wide availability and ease of eating ultra-processed and packaged foods, the lack of availability of fresh whole foods as seen in food deserts, other behavioral patterns, and the inability to sustain behavior and lifestyle changes. Losing weight remains a significant challenge for many patients. While medications or bariatric procedures are promising for some patients, there is also a growing movement and research to support incorporating health coaches to help patients with behavior change, which includes changing diet quality and patterns, increasing exercise, reducing stress, and improving sleep quality. Lifestyle changes are essential to continue, even if patients have bariatric surgery or are on medications, to help preserve lean mass and maintain weight. Given the morbidity and mortality associated with obesity, healthcare providers need to recognize overweight/obesity in our patients and refer them for appropriate counseling and programs to assist with weight loss, which will decrease the worldwide morbidity and mortality of cancer. Governments worldwide must ensure public education, the availability of higher quality food and provide coverage for weight loss programs, medications, and procedures that will ultimately be lifesaving.

5. Conclusions

Excess adiposity is a well-defined risk factor for multiple

malignancies, and there is growing evidence that weight loss achieved through different modalities, including lifestyle interventions, AOMs, and bariatric procedures, can decrease the risk of developing cancer. However, further prospective studies are needed to provide more robust evidence supporting weight loss strategies as a preventative intervention for cancer. Similarly, studies are needed to better characterize the amount of weight loss required to have the greatest benefit from these interventions, and whether specific populations should be targeted. Population-based interventions to promote a healthy weight should also be evaluated to determine if there is a potential role for weight loss as a primary prevention strategy for cancer.

- Obesity increases cancer risk in different anatomical locations through multiple mechanisms.
- Weight-loss interventions can decrease cancer risk in patients with excess adiposity, with the most evidence available for post-menopausal women.
- There is some conflicting data in terms of cancer protective effect after bariatric surgery for certain anatomical locations.

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Declaration of artificial intelligence (AI) and AI-assisted technologies

During the preparation of this work the authors did not use AI or AI-assisted technologies.

Declaration of competing interest

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